



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 31/565, 9/00, 47/10</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 92/14473</b> <b>(43) International Publication Date:</b> 3 September 1992 (03.09.92)
<b>(21) International Application Number:</b> PCT/GB92/00290 <b>(22) International Filing Date:</b> 19 February 1992 (19.02.92) <b>(30) Priority data:</b> 9103824.0 23 February 1991 (23.02.91) GB <b>(71) Applicant (for all designated States except US):</b> FISON'S AG [CH/CH]; Alte Steinhäuserstrasse 35, Postfach 5047, CH-6330 Cham (CH). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> SAUNDERS, Joy, Elaine [GB/GB]; 20 Harris Road, Chilwell, Nottingham NG9 4FB (GB). <b>(74) Agent:</b> WRIGHT, Robert, Gordon, McRae; Fisons plc, 12 Derby Road, Loughborough, Leicestershire LE11 0BB (GB).		<b>(81) Designated States:</b> AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK, DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> STEROID FORMULATIONS  <b>(57) Abstract</b>  An aqueous suspension formulation containing, as active ingredient, tiptredane. The formulation is useful for the treatment of conditions of the nose in which allergic or immune reactions play a contributory part.		

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Steroid formulations

This invention relates to novel pharmaceutical formulations, in particular to aqueous suspension formulations containing tipredane.

5 US Patent No 4,361,559 discloses a large number of 3-ketoandrostenes which are described as having useful anti-inflammatory activity, including useful activity in the topical treatment of allergy and asthma. This patent also specifically discloses (11 $\beta$ ,17 $\alpha$ )-17-(ethylthio)-9 $\alpha$ -  
10 fluoro-11 $\beta$ -hydroxy-17-(methylthio)-androsta-1,4-diene-3-one, which is known by the INN generic name tipredane.

We have now found that tipredane has useful anti-inflammatory activity when administered to the nose.

15 The most favoured vehicle for administering a drug to the nose is water as this is likely to give maximum bioavailability. However, tipredane has a water solubility below 0.002 mg/ml at room temperature. Although it may be possible to increase water solubility by the use of  
20 co-solvents or solubilising agents, such co-solvents and agents frequently cause nasal stinging and/or interact with the active ingredient. Attempts at increasing the aqueous solubility of tipredane using  $\beta$ -cyclodextrin derivatives were also unsuccessful.

25 Tipredane has a relatively poor oil solubility, which prevents the preparation of satisfactory emulsion formulations.

In general, powder formulations of non water soluble drugs for application to the nose are not favoured, in that  
30 the drug is being presented to the nose in a form that is unlikely to be readily bioavailable.

Propellant driven powder formulations are not favoured for tipredane, in that CFC driven formulations are unsatisfactory environmentally and HFC propellants are  
35 difficult to formulate.

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Surprisingly, we have now found that it is possible to formulate tipredane as an aqueous suspension and control nasal inflammatory conditions.

5 According to the invention there is provided an aqueous suspension formulation containing, as active ingredient, tipredane.

The formulation according to the invention is advantageous in that it is more efficacious, has a longer  
10 effect, produces fewer or less severe side-effects, or has other advantageous properties when compared with comparable formulations of other compounds or with other, known formulations of the active ingredient. In addition, the stability of the active ingredient may be enhanced in the  
15 formulation of the invention, which is surprising in view of the known tendency of the active ingredient to oxidise.

The active ingredient is preferably present in the formulation at a concentration of from 0.005% to 1.5% w/w, more preferably from 0.01 to 0.1% and especially from 0.2%  
20 to 0.4% w/w.

The formulation will generally contain a surfactant. Although ionic surfactants such as sodium lauryl sulphate may be used, we prefer the surfactant to be a non-ionic surfactant. Non-ionic surfactants that may be mentioned  
25 include glycol and glycerol esters, acetoglycerides, macrogol esters, macrogol ethers and sorbiton esters. We have found that the block copolymers of poloxyethylene-polyoxypropylene, known as poloxamers with the general formula  $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$ , in  
30 which a is 2 to 130 and b is 15 to 67 give particularly stable formulations.

We prefer poloxamers with an average molecular weight of between 4000 and 20,000, more particularly between 6000 and 15,000. A particularly preferred poloxamer that may be  
35 mentioned is that known as poloxamer 188 (poloxalkol) in

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which a in the general formula averages 75 and b averages 30. This has a molecular weight of about 8350.

The concentration of the surfactant in the formulation will depend inter alia on the particular surfactant used, but will in general be from 0.05% to 10% w/w, more preferably from 0.05% to 5% w/w, especially from 0.05% to 0.5% w/w. We have found that the use of such low concentrations of surfactant, eg about 0.1 %w/w, leads to particularly stable formulations which show improved resistance to oxidation.

The formulation may, if desired, contain an effective proportion of a pharmaceutically acceptable preservative or sterilising agent. Suitable preservatives include pharmaceutically acceptable quarternary ammonium compounds. The preferred preservatives amongst the quarternary ammonium compounds are the alkyl benzyl dimethyl ammonium chlorides and mixtures thereof, eg that known generically as 'benzalkonium chloride'.

The preservative may be used at a concentration of from about 0.005% to 0.10%, preferably 0.005% to 0.05%, eg about 0.01% w/w.

The formulation will generally also contain a pseudoplastic thixotropic viscosity modifying agent. Suitable thixotropic viscosity modifying agents which may be used include carboxy vinyl polymers, alginates, cellulose and its derivatives, for example hydroxypropyl methylcellulose and dispersible cellulose, which is a co-blend of microcrystalline cellulose and sodium carboxymethyl cellulose sold commercially as Avicel RC-591.

If present, the thixotropic viscosity modifying agent will be at a concentration at which the resulting viscosity of the formulation is suitable for its intended use. The viscosity of the formulation may be varied between quite wide limits (typically between 0.5 and 5.0% w/w) but, in

general, will be relatively low at high shear rates (to enable dispensing, eg as a spray from a conventional nasal pump) and relatively high at low shear rates.

5 We prefer the formulation according to the invention to be isotonic with the nasal mucosa. The formulation may therefore contain a tonicity adjusting agent, eg glycerol, at a concentration of from about 0.1% to 2.0%, more preferably 0.5% to 1.0% w/w.

10 The formulation may additionally contain conventional excipients eg electrolytes. A particularly preferred electrolyte is sodium chloride. Sodium chloride is useful as a flocculating agent and may also alter the tonicity of the formulation.

15 In general, the overall proportion and concentration of excipients may be varied within fairly wide ranges, provided that the resulting solution is stable and non-irritant when applied to the nasal tissues.

As a particularly preferred aspect of the invention, 20 there is provided an aqueous formulation comprising

- a) from 0.1 to 1.25% w/w of tipredane as active ingredient,
- b) from 0.05% to 10% w/w of a non-ionic surfactant,
- c) from 0.5 to 5% w/w of a thixotropic viscosity 25 modifying agent, and
- d) from 0.1 to 2.0% w/w of a tonicity adjusting agent.

The formulation of the invention may be made up, for example, by dispersing the active ingredient, using the surfactant as wetting agent, and dispersing or dissolving 30 the thixotropic viscosity modifying agent (if included) and other excipients (if included) in freshly distilled water, adding to this solution an aqueous solution of the preservative (if included), making the solution up to the desired volume with distilled water, and stirring. The 35 formulation is preferably made up under aseptic conditions.

According to another aspect of the invention there is provided a method of treatment of conditions of the nose, in which conditions allergic or immune reactions play a contributory part, which method comprises administration of  
5 a formulation according to the invention to a patient suffering from, or susceptible to, such a condition.

The dosage administered will of course vary with the condition to be treated and with its severity. However, in  
10 general, a dosage of about 400 $\mu$ g is indicated. The dose may be administered up to four times to each nostril at any one dosing session and from 1 to 4 times a days. We prefer to administer the formulation once or twice daily.

Conditions of the nose in which may be treated the  
15 method of the invention include seasonal rhinitis, eg hay fever; perennial rhinitis; nasal polyps and allergic manifestations of the nasopharynx.

The invention is illustrated, but in no way limited, by the following Example.

20 Example

Ingredients

	Active ingredient	0.308 w/w (equivalent to 400 $\mu$ g per actuation)
	Poloxamer 188	0.100
25	Sodium chloride Ph.Ew/USP	0.584
	Glycerol	1.000
	Benzalkonium chloride <sup>1</sup>	0.010
	Avicel RC-591	2.000
	Purified water Ph.Ew/BP/USP to	100.00

30 <sup>1</sup> added as a 50% w/v solution

The formulation has been found to be chemically and physically stable when using an identical vehicle containing tipredane at the following strengths:

35 0.0096% w/w (equivalent to 12.5 $\mu$ g per actuation)

- 0.0192% w/w (equivalent to 25 $\mu$ g per actuation)  
0.0385% w/w (equivalent to 50 $\mu$ g per actuation)  
0.0770% w/w (equivalent to 100 $\mu$ g per actuation)  
0.1540% w/w (equivalent to 200 $\mu$ g per actuation)  
5 0.692% w/w (equivalent to 800 $\mu$ g per actuation)  
1.231% w/w (equivalent to 1600 $\mu$ g per actuation)

#### Manufacturing process

Tipredane is dispersed in an aqueous solution of  
10 poloxamer 188, glycerol, sodium chloride and benzalkonium  
chloride. This is added to a dispersion of  
microcrystalline cellulose co-blend in water and mixed  
until homogeneous. The suspension is made to weight with  
more water before filling into bottles.

15 The tipredane is preferably micronised material, with  
a mean particle size of 5 $\mu$ g and not more than 20% by  
weight of the tipredane having a particle size of >  
10 $\mu$ m.

If necessary, the pH of the aqueous suspension can be  
20 adjusted by addition of acid or base as appropriate, to  
give a pH of between 4.5 and 7.5.

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## Claims

1. An aqueous suspension formulation containing, as active ingredient, tipredane.
2. A formulation according to claim 1 which includes a surfactant.
3. A formulation according to claim 2, wherein the surfactant is a non-ionic surfactant.
4. A formulation according to claim 2 or claim 3, wherein the surfactant is a poloxamer.
5. A formulation according to any one of the preceding claims, which includes a pharmaceutically acceptable preservative.
6. A formulation according to any one of the preceding claims, which includes a thixotropic viscosity modifying agent.
7. A formulation according to claim 6, wherein the viscosity modifying agent is cellulose or a derivative thereof.
8. A formulation according to any one of the preceding claims which is isotonic with the nasal mucosa.
9. An aqueous suspension formulation which comprises
  - a) from 0.1 to 1.25% w/w of tipredane as active ingredient,
  - b) from 0.05% to 10% w/w of a non-ionic surfactant,
  - c) from 0.5 to 5% w/w of a thixotropic viscosity modifying agent, and
  - d) from 0.1 to 2.0% w/w of a tonicity adjusting agent.
10. The use of tipredane in the manufacture of a medicament for the treatment of the nose in which allergic or immune reactions play a contributory part.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 92/00290

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5                      A 61 K 31/565                      A 61 K 9/00                      A 61 K 47/10		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	US,A,4868170 (SQUIBB) 19 September 1989, see the claims; column 1, lines 50-51 -----	1-10
A	EP,A,0073026 (SQUIBB) 2 March 1983, see the claims 1,18-23; page 5, lines 1-27 (cited in the application) -----	1-10
A	EP,A,0246652 (SYNTEX) 25 November 1987, see the claims -----	1-10
P,A <sup>-</sup>	WO,A,9111173 (FISONS) 8 August 1991, see the claims; page 7, lines 19-21,24-25; page 8, lines 1-4,9-15; page 10, example 2 -----	1-10
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents : <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
01-04-1992	28. 04. 92	
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EUROPEAN PATENT OFFICE	Nicole De Ble	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

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WO-A- 9111173	08-08-91	None	

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82